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TITLE: Cancer Associated Macrophage-Like (CAML) Cells to Enhance Detection of Early Stage Lung Cancer and Relapse after Definitive Treatment

PRINCIPAL INVESTIGATOR: Martin Edelman, M.D.

CONTRACTING ORGANIZATION:

Institute for Cancer Research
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Martin Edelman, M.D.

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13. SUPPLEMENTARY NOTES

14. ABSTRACT

The hypothesis of this study is that Cancer Associated Macrophage Like cells (CAMLs) can enrich for the presence of malignancy in patients with pulmonary nodules.
Specific Aims: 1. Determine the prevalence of CAMLS (+/- CTCs) in patients with indeterminate pulmonary nodules.; 2. Determine the positive and negative predictive value of CAMLS in patients with pulmonary nodules who undergo biopsy.; 3. Model combinations of clinical factors with the presence/absence of CAMLs to refine strategies for assessment of patients with pulmonary nodules.
Subjects will be drawn from pulmonary nodule and thoracic surgery clinics at the Fox Chase Cancer Center (FCCC) and VA Philadelphia (VA). CAMLs will be evaluated at the time of clinically indicated scans and correlated with the presence or absence of cancer. Patients with biopsy confirmed lung cancer within 12 months of the CAML test will be defined as "diseased"; otherwise, they will deemed as "disease free". Positive and negative predictive value of the test will be determined. Logistic regression will be used to assess the utility of this test after accounting for clinical factors and nodule characteristics. To date, the study has been activated and is accruing patients at FCCC and is undergoing IRB review at the VA.

15. SUBJECT TERMS

Lung cancer, pulmonary nodules, screening

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
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Principal Investigator: Martin Edelman, M.D.
Institution: Institute for Cancer Research
Grant Number: W81XWH-18-1-0196

INTRODUCTION:

Background and Hypothesis: The National Lung Screening Trial (NLST), for which the PI was a member of the endpoint verification committee, determined that low dose CT screening could decrease lung cancer death by 20%. However, almost 25% of screened subjects were determined to have pulmonary nodules with only 1.5% actually demonstrated to be malignant. This very high false positive rate results in several critical problems including the requirement for further testing (scans, biopsies), the potential of loss to follow-up, the possibility of false negative biopsy and the resultant patient stress and anxiety. Nodules between from .8-3.0 cm have been described as "indeterminate" and represent a management challenge. Recently we published preliminary data on the presence of CAMLs, specialized myeloid polyploid cells transiting the circulation of patients that have engulfed tumor cells or tumor material in a variety of malignancies and their clinical use in tracking cancer progression and evolution in response to therapy. CAMLs are rarely found in healthy controls and are easily identified by filtration methods.

Hypothesis: CAMLs can substantially enrich for the presence of malignancy in the population of patients with pulmonary nodules.

Specific Aims:

1. Determine the prevalence of CAMLS (+/- CTCs) in patients with indeterminate pulmonary nodules.
2. Determine the positive and negative predictive value of CAMLS in patients with pulmonary nodules who undergo biopsy.
3. Model combinations of clinical factors with the presence/absence of CAMLs to refine strategies for assessment of patients with pulmonary nodules.

Subjects will be drawn from pulmonary nodule and thoracic surgery clinics at the Fox Chase Cancer Center and VA Philadelphia. CAMLs will be evaluated at the time of clinically indicated scans and correlated with the presence or absence of cancer, as determined by clinically indicated biopsies. The proportion of patients with presence of CAMLs (CAML+), Positive Predictive Value (PPV), Negative Predictive Value (NPV), sensitivity and specificity of CAMLs (along with two-sided 95% confidence intervals (CI)) will be computed. Patients with biopsy confirmed lung cancer within 12 months of the CAML test will be defined as "diseased"; otherwise, they will deemed as "disease free". Logistic regression will be used to assess the utility of this test after accounting for clinical factors and nodule characteristics. We will also explore whether test performance differs among subsets of the population defined by demographic, clinical and nodule characteristics.

KEYWORDS: Lung cancer, pulmonary nodules, screening

ACCOMPLISHMENTS:

What were the major goals of the project?

1. To conduct an observational study of CAMLs in patients with indeterminate pulmonary nodules.
2. To determine the positive and negative predictive value of CAMLS in patients with pulmonary nodules who undergo biopsy.
3. Model combinations of clinical factors with the presence/absence of CAMLs to refine strategies for assessment of patients with pulmonary nodules.

What was accomplished under these goals?

At this time, we have met the following milestones:

1. Drafting of the clinical trial protocol.
2. IRB (Fox Chase) submission and approval of the protocol.
3. Activation and commencement of accrual to the protocol.

4. Creation of computerized data base for entry of data and future analysis.
5. Submission of the trial to the IRB at the Veterans Administration Hospital of Philadelphia/University of Pennsylvania.
6. To date there have been 450 subjects screened for the trial, all at FCCC. 53 subjects have been accrued to the study as of 07/25/2020. This study was open to enrollment 05/21/2019. The first patient was enrolled on 05/29/2019.
7. Approval of the protocol at the University of Pennsylvania (Dr. Vachani, co-PI). Established SOP for transfer of specimens from U of P to FCCC. The first subject was enrolled the last week of July 2020.
8. The VA Philadelphia (also under co-investigator Vachani) has not yet activated the study. This is due to COVID-19 restrictions on in-person care, particularly for screening visits (the primary location for discussing the study with potential subjects). There have also been restrictions placed by the VA on research only phlebotomy.

What opportunities for training and professional development has the project provided?
Nothing to report

How were the results disseminated to communities of interest?
Nothing to Report.

What do you plan to do during the next reporting period to accomplish the goals?
The focus of the next reporting period will be on accruing evaluable subjects to the study and processing samples obtained.

IMPACT:
What was the impact on the development of the principal discipline(s) of the project?
Nothing to report

What was the impact on other disciplines?
Nothing to Report.

What was the impact on technology transfer?
Nothing to Report.

What was the impact on society beyond science and technology?
Nothing to Report.

CHANGES/PROBLEMS:
Changes in approach and reasons for change
We have analyzed the reasons for screen failures. A major reason is the history of prior malignancy. We are considering a revision of the protocol to allow for prior malignancy that was treated with curative intent > or = to 3 years earlier (vs. 5).

Actual or anticipated problems or delays and actions or plans to resolve them
The COVID-19 crisis has severely impacted accrual. Screening for lung cancer and evaluation of pulmonary nodules are consider elective procedures and were completely halted throughout the state from mid-March 2020 until June 2020. Even at this time, many visits are being done through telehealth, which precludes enrollment to the study.

The above was discussed with the program officer (Dr. Michael Hall). We will likely need to request a no-cost extension at the end of the granting period.

Changes that had a significant impact on expenditures
Nothing to report

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents
Nothing to report

Significant changes in use or care of human subjects
Nothing to report

Significant changes in use or care of vertebrate animals.
N/A

Significant changes in use of biohazards and/or select agents
N/A

PRODUCTS:
Nothing to report

Publications, conference papers, and presentations

Journal publications. Nothing to report
Books or other non-periodical, one-time publications. Nothing to report
Other publications, conference papers, and presentations. Nothing to report

Website(s) or other Internet site(s)
N/A

Technologies or techniques
Nothing to report.

Inventions, patent applications, and/or licenses
Nothing to report

Other Products
Nothing to report

PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS
What individuals have worked on the project?

Name:	*Martin Edelman, M.D.*
Project Role:	*Principal Investigator*
Researcher Identifier (e.g. ORCID ID):	0000-0002-3752-0726
Nearest person month worked:	*1*
Contribution to Project:	*Dr. Edelman is the PI of the project and during this period, submitted and gained approval of the study, assembled the study team, designed the case report forms and coordinated all efforts related to the study.*
Funding Support:	

Name:	*Anil Vachani, M.D.*
Project Role:	*Site PI/Co-Investigator*

Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	1
Contribution to Project:	*Dr. Vachani has submitted the protocol to the VA/UPenn IRB and will begin accruing patients once activated.*
Funding Support:	

Name:	*Rohit Kumar, M.D.*
Project Role:	*Co-Investigator*
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	1
Contribution to Project:	Dr. Kumar supervises the recruitment efforts at Fox Chase.
Funding Support:	

Name:	*Dana Hagan*
Project Role:	*Clinical Research Coordinator*
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	*1*
Contribution to Project:	*Ms. Hagan has consented patients identified in the pulmonary clinic and collected and entered appropriate data. She has replaced Ms. Gudesblat who was the original clinical research coordinator for this project.*
Funding Support:	

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

Please see attached updated Other Support for Drs. Edelman and Anaokar. Changes are marked with a line in the right hand margin. There has been no change in the Other Support for Drs. Kumar and Vachani.

What other organizations were involved as partners?

Organization Name: VA Philadelphia (University of Pennsylvania)
Location of Organization: Philadelphia, PA
Partner's contribution to the project *(identify one or more)*

Financial support: N/A
In-kind support: N/A
Facilities: The VA pulmonary clinic facilities (and possibly U Penn) will serve as the sites for evaluation and recruitment of patients.
Collaboration: See above.
Personnel exchanges: N/A
Other: N/A

SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS: Not applicable.

QUAD CHARTS: Not applicable.

APPENDICES: Award Chart is attached.

Other Support

Edelman, Martin J.

Remaining salary support from clinical activities.

CURRENT

(PI: Edelman) 1/1/2020 - 12/31/2020 5.0%
SWOG-CTP $10,999 0.60 calendar
SWOG Lung-MAP Sub-Study
This project provides support to Dr. Edelman for oversight of the Lung-Map master protocol and substudy activities.

Procuring Contracting/Grants Officer: Johanna Horn, CEO, The Hope Fdn, 24 Frank Lloyd Wright Dr., PO Box 483, Ann Arbor, MI 48106, 734-998-6890

U10 CA180868 (PI: Wolmark/Curran/Mannel, NRG Onc) 3/1/2019 - 2/28/2025 5.0%
NIH $3,279 (Partial Salary) 0.60 calendar
NCI National Clinical Trials Network (NCTN) - Network Group Operations Centers
This project is a subcontract to the NRG Oncology Foundation and provides support to Dr. Edelman as Co-Chair of the Lung Cancer Committee.

Procuring Contracting/Grants Officer: Stephen Shephard, Nova Tower 2, Two Allegheny Ctr, Ste 1200, Pittsburgh, PA 151212, 412-339-5310

W81XWH-18-1-0196 (PI: Edelman) 7/15/2018 - 7/14/2021 5.0%
DOD $158,804 0.60 calendar
Cancer Associated Macrophage-Like (CAML) Cells to Enhance Detection of Early Stage Lung Cancer and Relapse after Definitive Treatment
The major goals of this project are to: 1) Determine the prevalence of CAMLS in patients with pulmonary nodules; 2) Determine the positive and negative predictive value of CAMLS in patients with pulmonary nodules who undergo biopsy; and 3) Model combinations of clinical factors with the presence/absence of CAMLs to refine strategies for assessment of patients with pulmonary nodules.

Procuring Contracting/Grants Officer: Danielle Reckley, USAMRAA, 830 Chandler St., Fort Detrick, MD 21702, 301-619-1139

P30 CA006927 (PI: Fisher) 8/12/2016 - 7/31/2021 15.0%
NIH No Salary 1.80 calendar
Comprehensive Cancer Center Program at Fox Chase
The major goal of this Cancer Center Support Grant is to provide partial salary support for professional personnel, including senior and program leadership, administration, planning and evaluation, and developmental funds, as well as support for 5 established peer-reviewed Research Programs, 12 Shared Research Resources and 2 Support Elements.

Procuring Contracting/Grants Officer: Candace Cofie, 9609 Medical Center Dr., Bethesda, MD 20892, 240-276-6317

OVERLAP

None

Other Support

Anaokar, Jordan

Remaining salary support from clinical sources.

CURRENT

R03 CA219722 (PI: Vijayvergia/Anaokar)	1/1/2020 - 12/31/2021		6.8%
NIH	$53,000	0.82	calendar

Systematic Study of Variations in Imaging Techniques and Response Criteria for Well Differentiated Pancreatic Neuroendocrine Tumors (Multi-PI)

The major goals of this project are to: 1) Assess the quality of multiphasic CT scans and estimated radiation dose per scan in PanNETs and compare findings based on clinical setting and assess the inter-reader variability in response assessment of PanNETs per RECIST 1.1; and 2) Assess alternate response criteria in PanNETs, correlating response classification at the time of first evaluation with progression free survival (PFS).

Procuring Contracting/Grants Officer: Sarah Lee, 9609 Medical Center Dr., BG0609 RM 2W552, Rockville MD 20850, 240-276-6280

W81XWH-18-1-0196 (PI: Edelman)	7/15/2018 - 7/14/2021		5.0%
DOD	Salary only	0.60	calendar

Cancer Associated Macrophage-Like (CAML) Cells to Enhance Detection of Early Stage Lung Cancer and Relapse after Definitive Treatment

The major goals of this project are to: 1) Determine the prevalence of CAMLS in patients with pulmonary nodules; 2) Determine the positive and negative predictive value of CAMLS in patients with pulmonary nodules who undergo biopsy; and 3) Model combinations of clinical factors with the presence/absence of CAMLs to refine strategies for assessment of patients with pulmonary nodules.

Procuring Contracting/Grants Officer: Danielle Reckley, USAMRAA, 830 Chandler St., Fort Detrick, MD 21702, 301-619-1139

OVERLAP

None

LC170215: Cancer Associated Macrophage-Like (CAML) Cells to Enhance Detection of Early Stage Lung Cancer and Relapse after Definitive Treatment

Edelman, Martin

PI: Martin Edelman, M.D., Institute for Cancer Research, PA **Budget:** $672,969

Topic Area: Lung Cancer **Mechanism:** Translation Research Partnership Award

Research Area(s): 0701 – Clinical Biomarkers **Award Status:** 07/15/2018 – 07/14/2021

Study Goals: Cancer Associated Macrophage Like (CAML) cells are a recently discovered immune cell that appears early in the course of malignancy. Indeterminate pulmonary nodules are commonly seen and present a clinical problem regarding the timing and intensity of evaluation for malignancy. Our hypothesis is that CAMLs can substantially enrich for the presence of malignancy in the population of patients with pulmonary nodules and allow for earlier diagnosis in malignancy. Conversely, the absence of CAMLs would predict for absence of malignancy and prevent unnecessary procedures.

Specific Aims:

1. To conduct an observational study of CAMLs in patients with indeterminate pulmonary nodules.
2. To determine the positive and negative predictive value of CAMLS in patients with pulmonary nodules who undergo biopsy.
3. Model combinations of clinical factors with the presence/absence of CAMLs to refine strategies for assessment of patients with pulmonary nodules.

Key Accomplishments and Outcomes:

Publications: none to date

Patents: none to date

Funding Obtained: none to date